Complete Summary

GUIDELINE TITLE

Systemic adjuvant therapy for patients at high risk for recurrent melanoma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Verma S, Quirt I, McCready D, Bak K, Charette M, Iscoe N, Melanoma Disease Site Group. Systemic adjuvant therapy for patients at high risk for recurrent melanoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Aug 30. 39 p. (Evidence-based series; no. 8-1). [61 references]

GUIDELINE STATUS

This is the current release of the guideline.

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

High-risk malignant melanoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Dermatology
Internal Medicine
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate systemic therapy for patients who have been rendered disease-free following resection of cutaneous melanomas and who are at high risk for subsequent recurrence

TARGET POPULATION

Adult patients with high-risk malignant melanoma who are rendered disease-free following resection. High risk is defined as patients in the following clinical states who have been rendered disease free by surgery:

- Primary melanoma with tumour thickness $\geq$4.0 mm or level V invasion
- Primary melanoma with in-transit metastases
- Primary melanoma with regional lymph node metastases that are clinically apparent or detected at elective lymph-node dissection
- Regional lymph node recurrence
- Involved nodes were excised but there was no known primary melanoma.

Note: The target population also includes those patients who would now be classified as American Joint Committee on Cancer stage IIB, IIC, and III.

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant Therapy for High-Risk Melanoma

High-dose interferon

Considered but not recommended: low-dose interferon, levamisole, vaccines, and chemotherapy

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease-free survival
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The MEDLINE (1980 through July 2005), CANCERLIT (1983 through 2004), EMBASE (1980 to 2005 week 32) and Cochrane Library (2005, Issue 2) databases were systematically searched. The search terms included the Medical Subject Heading (MeSH) terms melanoma/th, melanoma/dt, and clinical trial, and the text words random: and adjuvant. A search was also done for published practice guidelines, meta-analyses, and reviews. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (www.cancer.gov/search/clinical_trials/) and the proceedings of the 1996-2005 meetings of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. Articles found by the searches, cited in the relevant papers, or known to members of the Melanoma Disease Site Group were retrieved and reviewed.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials (RCT) of systemic therapies for the adjuvant treatment of patients with melanoma. Prior to the literature search, four types of treatments were identified as relevant to the guideline question: levamisole, interferon, vaccines, and chemotherapy.
2. Trials had to include patients at high risk of recurrence, but the study population did not need to be restricted to that group of patients. For this report, high risk is defined by American Joint Committee on Cancer (AJCC) stages IIB and III (please see Appendix 1 of the original guideline document for staging information) and includes primary tumours $\geq$4.00 mm thick, regional lymph-node metastases that are clinically apparent at presentation or are detected at lymph node dissection, and regional lymph node recurrence. All studies were conducted under the previous AJCC staging system. We attempt to define how patients under the new AJCC staging system should be considered, recognizing that the views expressed cannot be based on data but are the guideline developer's view of the information available.
3. Practice guidelines, meta-analyses, and systematic reviews of adjuvant treatment of malignant melanoma were also eligible for review.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Papers published in a language other than English were not considered.
3. Bacillus Calmette-Guérin (BCG), Corynebacterium parvum, transfer factor, vitamin A, and megestrol acetate have been investigated in the past as adjuvant therapy. However, there does not appear to be any ongoing interest in these agents. Trials involving these agents have been excluded in this systematic review.

NUMBER OF SOURCE DOCUMENTS

The following were eligible for inclusion in the systematic review of the evidence on adjuvant therapy: 13 trials of interferon, four trials of levamisole, nine trials of vaccines, and ten trials investigating chemotherapy. In addition, one report of a consensus development conference, two meta-analyses of interferon alpha therapy, one systematic review of adjuvant interferon alpha therapy, and one trial of chemotherapy plus interferon were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Published guidelines for performing meta-analysis deal with issues related to the comparability among studies of the questions being addressed, the patient populations, the interventions, and the outcomes. The majority of the trials selected for inclusion in this report addressed a common question, namely: Does the therapy under investigation, when given as adjuvant treatment, improve survival, compared with no treatment? Similar patient groups, albeit with varying risks of recurrence by virtue of entry criteria, participated in the randomized trials. Few trials were restricted to patients at high risk of recurrence (i.e., lesion depth 4.0 mm or greater or completely resected regional nodal metastases). For trials enrolling patients with a range of risks, survival results were not reported separately for the high-risk subgroup. The treatments evaluated fall into the following four distinct groups of interventions: interferons, levamisole, vaccines, and chemotherapy. Dose or schedule varied within each type of treatment. The majority of studies used an observation-only control arm rather than a placebo control, while some compared two active treatments.

In contrast to a published systematic review by Lens and Dawes, the guideline developers pooled the results from the three published Eastern Cooperative Oncology Group (ECOG) trials of high-dose interferon alpha therapy. However, the most recent ECOG trial (1694) had a vaccine as the intervention arm and interferon as the control arm. They pooled the results with and without ECOG 1694 and discuss the advisability of this approach in the Interpretive Summary section of the original guideline document. Results were pooled across studies using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview© Update Software). Pooled results are expressed as relative risks (also known as risk ratios) for mortality (with 95% confidence interval [CI]) such that a relative risk less than 1.0 favours the active treatment group. Data were analyzed using the random effects model. All significance tests are two-sided. Ideally, a meta-analysis would be restricted to high-risk patients as defined above. However, most of the studies were not limited to that group of patients. Although attempts were made to derive information for that group from the study reports or to obtain results directly from investigators, limited relevant data were available.

In addition, guideline developers were able to pool mortality data within two of the other groups of therapies (levamisole and chemotherapy). They did not pool results from trials of vaccines. The vaccine trials studied a variety of vaccines that differed in the postulated mechanisms by which they were hypothesized to exert their immunomodulatory effects. Therefore, the guideline developers do not believe that pooling the results from those trials is appropriate.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Guideline Development

This practice guideline report was developed by the Program in Evidence-based Care (PEBC) of Cancer Care Ontario, using the methods of the Practice Guidelines Development Cycle. Evidence was selected and reviewed by one member of the PEBC's Melanoma Disease Site Group (DSG) and methodologists.

The practice guideline report is a convenient and up-to-date source of the best available evidence on systemic adjuvant therapy for patients at high risk for recurrent melanoma, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

A practice guideline report on systemic adjuvant therapy for patients at high risk for recurrent melanoma was originally completed in 1998 and published on the Web site. With the publication of further relevant literature on adjuvant therapy and the adoption of a new staging system for cutaneous melanoma, the

Melanoma DSG has rewritten its 1998 report. This document replaces that 1998 report.

Disease Site Group Consensus Process

The members of the Melanoma DSG reviewed the rewritten document at a meeting held in September 2002. The group unanimously agreed that interferon has activity in the adjuvant setting. However, one member of the DSG objected to the word "offered" in the Key Recommendation, pointing out that the issue of adjuvant interferon is controversial and that the use of the word "offered" precludes further clinical trials being undertaken. This member suggested alternate wording for the recommendation: "We recommend that interferon therapy be discussed with the high risk patient. It may be used as adjuvant treatment, provided that each patient has been made aware of the controversies, relative risks, benefits, and costs of this therapy and wishes to proceed." The group noted this objection but decided to let the Key Recommendation stand as currently written, to be reviewed by practitioners in Ontario.

Another issue raised at the meeting of the Melanoma DSG concerned the new American Joint Committee on Cancer (AJCC) staging system, which highlights the presence of ulceration as an important prognostic factor. Under the new staging system, patients with lesions between 2.0 and 4.0 mm with ulceration have the same prognosis as patients with lesions greater than 4.0 mm without ulceration. None of the trials included in this document were conducted under the new staging system. However, the group felt that new trials based on the new staging criteria were unlikely to be undertaken. For this reason, the Target Population has been amended to include patients with shallower, ulcerated lesions. The DSG sought input from Ontario practitioners about the appropriateness of including these new patients when this document was circulated for practitioner feedback.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Melanoma Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 91 practitioners in Ontario (50 general surgeons, 20 plastic surgeons, 18 medical oncologists, and three dermatologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 11, 2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Melanoma Disease Site Group (DSG) reviewed the results of the survey. Forty-three responses were received out of the 91 surveys sent (47% response rate).

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Seven of the 12 members of the PGCC returned ballots. Four PGCC members approved the practice guideline report as written, two members approved the report with suggestions for consideration by the Melanoma DSG, and one member approved the report conditional on the Melanoma DSG addressing specific concerns. The main suggestion of the PGCC member was that the DSG outline the dose and schedule of high-dose interferon being recommended.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

It is recommended that high-dose interferon alpha therapy (20 $X10^6$ $U/m^2/d$ intravenously five days/week for four weeks, then 10 X 10^6 U/m^2 subcutaneously three times weekly for 48 weeks) be discussed and offered to the high-risk group as defined in the guideline question (see "Target Population" field). It may be used as adjuvant treatment, provided that each patient has been made aware of the relative risks, benefits, and costs of this therapy and wishes to proceed.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Familiarity with and appropriate use of systemic therapy options for patients who have been rendered disease-free following resection of cutaneous melanomas and who are at high risk for subsequent recurrence

POTENTIAL HARMS

Sixty-seven percent of patients who received high-dose interferon in the Eastern Cooperative Oncology Group (ECOG) 1684 trial experienced severe (grade 3 or greater) toxicity with 9% of patients having life-threatening toxicity. Thirty-seven percent of patients on high-dose interferon in ECOG 1684 and 59% in ECOG 1690 had dose reductions or delays in treatment because of toxicity. Two deaths due to interferon, linked to inadequate monitoring of liver function tests in those patients, occurred early in ECOG 1684. No further treatment-related mortality at this dose has been described in that or subsequent trials.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Patients and practitioners should be aware that there have been four randomized trials of high-dose interferon alpha in patients at high risk for recurrent melanoma. The evidence from the randomized trials is conflicting. The Eastern Cooperative Oncology Group (ECOG) 1684 trial detected a significant improvement in overall survival, but a subsequent large randomized trial (ECOG 1690) failed to find any survival benefit for interferon compared with observation. Results from a third trial (ECOG 1694) that compared high dose interferon with a melanoma vaccine demonstrated a significant survival benefit for interferon. A fourth trial of high-dose interferon over a shorter treatment time failed to detect any benefit.
- Practitioners should be aware that elderly patients (age 65 and older) were underrepresented in the high-dose interferon trials. Given the toxicities of interferon, particularly in the presence of other significant comorbidities, caution is advised.
- The role of adjuvant interferon in patients with micrometastases as determined solely through sentinel lymph node dissection has not been defined and is the subject of ongoing trials. However, until such data is available, it is reasonable to discuss the benefits and risks of interferon therapy with such patients, particularly in those with more than one microscopically involved lymph node at the time of dissection, who would not be eligible for the ongoing randomized controlled trial.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 May 27 (revised 2005 Aug 30)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Melanoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Melanoma Disease Site Group members were asked to disclose potential conflict of interest information; no conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Systemic adjuvant therapy for patients at high risk for recurrent melanoma: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. The summary was updated by ECRI on August 10, 2001 and verified by the guideline developer as of August 22, 2001. This NGC summary was updated by ECRI on March 20, 2003. The information was verified by the guideline developer on May 8, 2003. This NGC summary was most recently updated on September 27, 2004. The updated

information was verified by the guideline developer on October 20, 2004. This NGC summary was updated by ECRI on June 29, 2006. The updated information was verified by the guideline developer on July 7, 2006.

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